

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY  
WASHINGTON, D.C. 20460



OFFICE OF  
PREVENTION, PESTICIDES AND  
TOXIC SUBSTANCES

OFFICIAL RECORD  
HEALTH EFFECTS DIVISION  
DART MEMORANDUMS  
7/27/06

**MEMORANDUM**

TXR NO: 0054361

DATE: September 20, 2006

SUBJECT: BAS 800H: Early Mortality in the Mouse Cancer Study

PC Code: 118203; DP Barcode: 332665

FROM: Jessica Kidwell, Executive Secretary  
Dose Adequacy Review Team  
Health Effects Division (7509P)

Handwritten signature of Jessica Kidwell in black ink.

THROUGH: Jess Rowland, Chair  
Dose Adequacy Review Team  
Health Effects Division (7509P)

Handwritten signature of Jess Rowland in black ink.

TO: Joanne Miller, Product Manager  
Tracy White, Reviewer  
Herbicide Branch, Registration Division (7505P)

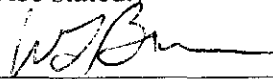
In response to BASF Toxicologist Jim Sherman's emails (attached) regarding early mortality in the mouse carcinogenicity study (using C57BL/6NCrl mice supplied by Charles River, Germany), the DART recommends that if 75% mortality is noted in any male group (control or treated), then an early sacrifice should be performed in all groups of male mice. The female mice should continue until scheduled termination unless a similar increase in mortality is seen.

This memo documents the USEPA DART's approval for termination of this study before 18 full months of treatment as described above.

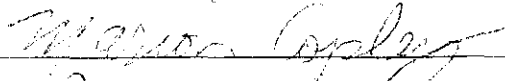
*Note to Registrant:* Please reference this DART memo in the final study submission to EPA as justification for this action.

**DART Members in Attendance at the September 19, 2006 Meeting:** (Signature indicates concurrence with the report unless otherwise stated.)

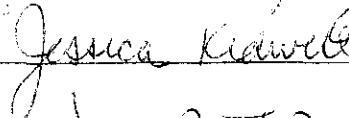
William Burnam



Marion Copley



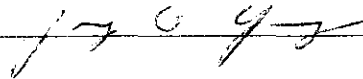
Jessica Kidwell



Jess Rowland



Yung Yang



ATTACHMENTS: EMAILS FROM JIM SHERMAN, BASF TO JESS ROWLAND,  
EPA ON 9/18/06 AND 9/19/06

----- Forwarded by Jess Rowland/DC/USEPA/US on 09/18/2006 03:37 PM -----

**James H Sherman**

**<james.sherman@basf.com>** To: Jess Rowland/DC/USEPA/US@EPA

cc

09/18/2006 03:33 PM Subject: Re: Early Mortality in the Mouse Cancer Study  
with BAS 800 H

James H Sherman, Ph.D., DABT  
Toxicologist Sr

Phone: 1-919-547-2930  
E-mail: james.sherman@basf.com  
Postal Address:

BASF - The Chemical Company

To: [rowland.jess@epa](mailto:rowland.jess@epa).  
cc: Charles E Hastings /NVA/RTP/BASF-CORP/BASF@

09/07/2006 10:53 AM  
Subject: BASF-CORP  
Early Mortality in the Mouse Cancer Study with BAS 800 H

Jess:

As discussed this morning, we are experiencing some early mortality in the mouse carcinogenicity study with BAS 800 H. The early mortality seems to be due to the specific mouse strain we are using, and is not a compound-specific effect, as we see the comparable results in other mouse studies that were initiated in the same time frame. In an effort to ensure the acceptability of our studies, we would appreciate some general guidance from the USEPA.

Pursuant to our meetings with the DART committee, we initiated dosing in the BAS 800 H mouse study on May 10, 2005. After approximately one year of treatment an increased incidence of unscheduled deaths began to be recorded in mice in control and all treatment groups. After 16 months of treatment, survival in all treatment groups is >50%. As such, the study has met the acceptance criteria for no less than 50% survival at 15 months. However, because the rate of unscheduled deaths is increasing, we have some concern that >25% survival may not be achieved in all treatment groups if the terminal sacrifice is carried out on November 8 and 9, as scheduled.

The specific questions we have are:

- 1) If 75% mortality is noted in any group (control or treated), should we perform an early sacrifice? At this point, we feel that would not happen until the mice had been treated for at least 17 months.
- 2) Since we do have an extra treatment group in this study (4 treated and a control group for each sex), is it better to examine survival of all control treatment groups rather than focusing on a single group? For

example, if only the survival in the second highest dose group in a single sex drops below 25%, should we just continue the study?

3) If we terminate the study before the scheduled sacrifice at 18 months, is there a formal mechanism whereby we can gain USEPA approval for terminating the study before 18 full months of treatment?

In an effort to help in your assessment, I have included the most recent interval mortality report for the study.

Thank you for your continuing guidance as we proceed in our product development program.

Best regards,

Jim

(See attached file: 01177.pdf)

James H. Sherman, Ph.D., DABT  
Toxicologist Sr

Phone: -919-547-2930  
E-mail: james.sherman@basf.com  
Postal Address:

BASE - The Chemical Company

 BASF

 BASF

01177.pdf



Study: 87C0414/01177

Group

Print Date: 07-Sep-2006  
Print Time: 10:02:04  
Table : 1A  
Page : 1

Group	No. of Animals	Period Ending (Day)	0 ppm				5 ppm				25 ppm				75 ppm				150 ppm			
			Sch	Unsch prd	Avl Tot	Sch	Unsch prd	Avl Tot	Sch	Unsch prd	Avl Tot	Sch	Unsch prd	Avl Tot	Sch	Unsch prd	Avl Tot	Sch	Unsch prd	Avl Tot		
	28				50			50			50			50			50			50		
	56				50			50			50			50			50			50		
	84				50			50			50			50			50			50		
	112				50			50			50			50			50			50		
	140				50			50			50			50			50			50		
	168				50			50			50			50			50			50		
	196				50			50			50			50			50			50		
	224				50			50			50			50			50			50		
	252				50			50			50			50			50			50		
	280				50			50			50			50			50			50		
	308		2%		49			48			48			48			48			48		
	336				49			48			48			48			48			48		
	364				49			48			48			48			48			48		
	392		2%		48			47			46			46			46			46		
	420		2%		47			46			45			45			45			45		
	448		4%		45			44			43			43			43			43		
	476		9%		41			40			39			39			39			39		
	483		2%		40			39			38			38			38			38		
	484		3%		39			38			37			37			37			37		

7

----- Forwarded by Jess Rowland/DC/USEPA/US on 09/19/2006 08:42 AM -----

**James H Sherman**  
<james.sherman@basf.com>  
09/19/2006 08:18 AM  
To: Jess Rowland/DC/USEPA/US@EPA  
cc  
Subje Fw: BAS 800 H: mouse study; Mortality  
ct

Jess:

Below is the most recent mortality data from the mouse study with BAS 800 H.

Thanks for working with me on this.

Best regards,

Jim  
James H Sherman, Ph.D., DABT  
Toxicologist Sr

Phone: 1-919-547-2930  
E-mail: james.sherman@basf.com  
Postal Address:

BASF - The Chemical Company

----- Forwarded by James H Sherman/APD/RTP/BASF-CORP/BASF on 09/19/2006 08:15 AM -----

	Georgia Cunha/BA SF-AG/BA	
To	SF@EUROP E	James H Sherman/APD/RTP/BASF-
CORP/BASF@B		ASF-CORP
	09/19/20	
cc	06 04:20 AM	Werner Mellert/ZH/BASF-AG/BASF@EUROPE
Subject		BAS 800 H: mouse study; Mortality



Information from 18/09:

males:	Gr.0/ 0	ppm = 46%
	Gr.1/ 1	ppm = 58%
	Gr.2/ 5	ppm = 42%
	Gr.3/25	ppm = 30%
	Gr.4/75	ppm = 30%

females:	Gr.0/ 0	ppm = 28%
	Gr.2/ 5	ppm = 30%
	Gr.3/ 25	ppm = 36%
	Gr.4/ 75	ppm = 32%
	Gr.5/150	ppm = 16%

Regards,

Georgia Cunha  
Mechanistic Toxicology

Phone: +49 621 60-58160, E-Mail: georgia.cunha@basf.com  
Postal Address: BASF Aktiengesellschaft, GV/TD - Z470, D-67056  
Ludwigshafen, Germany

BASF - The Chemical Company

BASF Aktiengesellschaft, Registered Office: 67056 Ludwigshafen, Germany  
Companies' Register: Amtsgericht Ludwigshafen, HRB 3000  
Board of Executive Directors:  
Juergen Hambrecht, Chairman; Eggert Voscherau, Vice Chairman;  
Kurt W. Bock, Martin Brudermueller, John Feldmann, Andreas Kreimeyer,  
Klaus Peter Loebbe, Stefan Marcinowski, Peter Oakley  
Chairman of the Supervisory Board: Juergen Strube



13544

R132691

**Chemical:** Benzamide, 2-chloro-5-[3,6-dihydro-3-methyl-2,6-dioxo-4-(trifluoromethyl)-1(2H)-pyrimidinyl]-4-fluoro-N-[[methyl(1-methylethyl)amino]sulfonyl]-

**PC Code:**  
118203

**HED File Code:** 13000 Tox Reviews  
**Memo Date:** 9/20/2006  
**File ID:** TX0054361  
**Accession #:** 412-07-0024

**HED Records Reference Center**  
11/9/2006

